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(to be used for all correspondence after initial filing)

Application Number	09/989,722
Filing Date	November 19, 2001
First Named Inventor	Ashkenazi, et al.
Group/Art Unit	1647
Examiner Name	Wegert, Sandra
Attorney Docket Number	39780-2730P1C63

Total Number of Pages in This Submission: 21

ENCLOSURES *(check all that apply)*

- [X] **Fee Transmittal Form**
  - [ ] Fee Attached
- [ ] Response to Office Communication
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  - [ ] Version With Markings Showing Changes
  - [ ] Affidavits/declaration(s)
- [X] **Extension of Time Request (3-month EOT = $1,020.00)**
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
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- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, by Assignee to Exclusion of Inventor Under 37 C.F.R. §3.71 With Revocation of Prior Powers
- [ ] Terminal Disclaimer
- [ ] Small Entity Statement
- [ ] Request for Refund
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
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SIGNATURE OF APPLICANT, ATTORNEY OR AGENT

Firm or Individual name	HELLER EHRMAN LLP	GINGER R. DREGER, ESQ. (Reg. No. 33,055)	
	275 Middlefield Road, Menlo Park, California 94025	Telephone: (650) 324-7000	Facsimile: (650) 324-0638
Signature			
Date	AUGUST 30, 2005	Customer Number:	35489

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Effective 12/08/2004. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($) 1,520.00

Complete if Known	
Application Number	09/989,722
Filing Date	November 19, 2001
First Named Inventor	Ashkenazi, et al.
Examiner Name	Wegert, Sandra
Art Unit	1647
Attorney Docket No.	39780-2730P1C63

METHOD OF PAYMENT (check one)

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FEE CALCULATION

1. BASIC FILING FEE

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description	Fee Paid
1001	300	2001	150	Utility filing fee	
1002	350	2002	175	Design filing fee	
1003	550	2003	275	Plant filing fee	
1004	790	2004	395	Reissue filing fee	
1005	200	2005	100	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		x		=	
Independent Claims		-3** =		x		=	0
Multiple Dependent						=	0

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description
1202	50	2202	25	Claims in excess of 20
1201	200	2201	100	Independent claims in excess of 3
1203	360	2203	180	Multiple dependent claim, if not paid
1204	200	2204	100	**Reissue independent claims over original patent
1205	50	2205	25	**Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	120	2251	60	Extension for reply within first month	
1252	450	2252	225	Extension for reply within second month	
1253	1,020	2253	510	Extension for reply within third month	1,020.00
1254	1,590	2254	795	Extension for reply within fourth month	
1255	2,160	2255	1,080	Extension for reply within fifth month	
1401	500	2401	250	Notice of Appeal	
1402	500	2402	250	Filing a brief in support of an appeal	500.00
1403	1,000	2403	500	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	500	2452	250	Petition to revive - unavoidable	
1453	1,500	2453	750	Petition to revive - unintentional	
1501	1,400	2501	700	Utility issue fee (or reissue)	
1502	800	2502	400	Design issue fee	
1503	1,100	2503	550	Plant issue fee	
1460		1460		Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	790	2809	395	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	790	2810	395	For each additional invention to be examined (37 CFR 1.129(b))	
1801	790	2801	395	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)_____

* Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($)1,520.00

SUBMITTED BY

Name *(Print/Type)*	GINGER R. DREGER, ESQ.	Registration No. *(Attorney/Agent)*	33,055	*Telephone*	650-324-7000
Signature		*Date*	AUGUST 30, 2005	Customer No. 35489	

Complete *(if applicable)*

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: Wegert, Sandra
Avi ASHKENAZI, et al.	Art Unit: 1647
Application Serial No. 09/989,722	Confirmation No: 1427
Filed: November 19, 2001	Attorney's Docket No. 39780-2730 P1C63
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	**Customer No. 35489**

EXPRESS MAIL LABEL NO. : EL 976 552 374 US
DATE MAILED: August 30, 2005

ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANTS' BRIEF

MS: APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

This Appeal Brief, filed in connection with the above captioned patent application, is responsive to the Final Office Action mailed on October 1, 2004. A Notice of Appeal was filed herein on March 31, 2005. This brief is timely filed with a request for a three month Extension of Time with required fees. Appellants hereby appeal to the Board of Patent Appeals and Interferences from the final rejection in this case.

The Commissioner is authorized to charge any fees which may be required, including extension fees, or credit any overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C63**.

09/02/2005 BABRAHA1 00000035 081641 09989722
01 FC:1253 1020.00 DA

09/02/2005 BABRAHA1 00000035 081641 09989722
02 FC:1402 500.00 DA

The following constitutes the Appellants' Brief on Appeal.

I. REAL PARTY IN INTEREST

The real party in interest is Genentech, Inc., South San Francisco, California, by an assignment of the parent application, U.S. Serial No. 09/941,992 recorded November 16, 2001, at Reel 012176 and Frame 0450.

II. RELATED APPEALS AND INTERFERENCES

The claims pending in the current application are directed to a polypeptide referred to herein as "PRO1153". There exist two related patent applications, (1) U.S. Serial No. 09/997,683, filed November 15, 2001 (containing claims directed to antibodies to the PRO1153 polypeptide), and (2) U.S. Serial No. 09/997,440, filed November 15, 2001 (containing claims directed to PRO1153 polypeptides). These two related applications are pending and are being examined by the same Examiner.

III. STATUS OF CLAIMS

Claims 124, 129-131 and 135-145 are in this application.

Claims 1-123, 125-128 and 132-134 have been canceled.

Claims 124, 129-131 and 135-145 stand rejected and Appellants appeal the rejection of these claims.

A copy of the rejected claims in the present Appeal is provided in the Claims Appendix.

IV. STATUS OF AMENDMENTS

In an Amendment filed on December 23, 2004 after the mailing of the Final Office of October 1, 2004, Claims 119-123 were canceled and Claims 124 and 139 were amended to more clearly claim what the Appellants always believed was the claimed subject matter in the present application. The Advisory Action mailed April 27, 2005 indicated that these amendments were entered for purposes of this appeal. Hence, Claims 124, 129-131 and 135-145 are currently pending and are under Appeal in this case, and, the rejection under 35 U.S.C. §112, first paragraph to Claims 119-123 for not satisfying the written description requirement are moot. The outstanding rejections are addressed with respect to these pending claims.

Further, in an Amendment filed on August 25, 2005 after the mailing of the Final Office of October 1, 2004, a declaration by Audrey Goddard, Ph.D. was filed. Entry of this declaration, was indicated as acceptable in a telephone conference with Examiner Wegert on August 24, 2005 for the purposes of this appeal.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent Claim 124 is directed to an isolated nucleic acid of SEQ ID NO: 350; the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 350; or the full-length coding sequence of the cDNA deposited under ATCC accession number 209982, and encodes for the PRO1153 polypeptide. The PRO1153 gene was shown for the first time to be significantly amplified in human lung adenocarcinomas or squamous cell carcinomas as compared to normal, non-cancerous human tissue controls (2.014 to 2.87 fold in two different lung primary tumors). This is set forth in the specification, at least in the 'Gene Amplification assay,' Example 170, page 539, line 19, to page 555, line 5 (specifically, see Table 9B, page 551). The profiles of various primary lung tumors used for screening the PRO polypeptide compounds of the invention in the gene amplification assay are summarized on Table 8, page 546 of the specification. This feature is carried by all claims dependent directly or indirectly from Claim 124, namely, Claims 129-138. Methods for selecting a host are generally set forth in the specification at, for example, in Examples 140-143 and page 376, line 12 onwards (Claims 137-138), and describes the expression of PRO nucleic acids in various host cells, including *E. coli*, yeast and Baculovirus-infected insect cells. Methods for selecting a vector are generally set forth in the specification at, for example, on page 378, line 8 (Claims 135 and 136).

Independent Claim 139 is directed to an isolated nucleic acid consisting of at least 30 nucleotide fragment of the nucleic acid sequence of SEQ ID NO: 350, or a complement thereof, that specifically hybridizes under highly stringent conditions to (a) the nucleic acid sequence of SEQ ID NO: 350 or a complement thereof; or (b) the full-length coding sequence of the cDNA deposited under ATCC accession number 209982 or a complement thereof and wherein the isolated nucleic acid molecule is suitable for use as a PCR primer or probe. Methods for using high stringent hybridization conditions recited in Claim 139 are provided, for example, on page 312, line 33 onwards. Pending Claims 140-145 depend from Claim 139. Methods for using polynucleotides encoding PRO as hybridization probes consisting of nucleotide fragments of

varying lengths is described at, for example, on page 285, line 11 onwards, and describes probes of at least 50 nucleotides (Claim 140), 60 nucleotides (Claim 141), 70 nucleotides (Claim 142), 80 nucleotides (Claim 143), 90 nucleotides (Claim 144) and 100 nucleotides (Claim 145).

Finally, the amino acid sequence of the native "PRO1153" polypeptide and the nucleic acid sequence encoding this polypeptide (referred to in the present application as "DNA59842-1502") are shown in the present specification as SEQ ID NOs: 351 and 350, respectively, and in Figures 246 and 245, respectively. Page 299, lines 34-37 of the specification provides the description for Figures 246 and 245. The isolation of cDNA clones encoding PRO1153 of SEQ ID NO:350 is described in Example 108, page 490 of the specification. The specification discloses that various portions of the encoded PRO1153 polypeptide is very proline rich ad has two transmembrane domains (see, for example, page 220-222, line 30 onwards).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether Claims 124, 129-131 and 135-145 should be accorded priority of provisional Application 60/141,037, filed 19 November, 2001.

2. Whether Claims 124, 129-131 and 135-145 satisfy the utility/ enablement requirement under 35 U.S.C. §101/112, first paragraph.

VII. ARGUMENTS

Summary of the Arguments

Issue 1: Priority

The instant application has not been granted the earlier priority date on the grounds that "although disclosing the same experimental assays as the instant specification, do not enable the instant invention and therefore do not impart Utility..."

Appellants submit that data derived from the Gene Amplification assay was first disclosed in U. S. Application Serial No. 60/141,037, filed 19 November, 2001 for the claimed PRO1153 encoding gene. Appellants further submit that, the same detailed reasons discussed below under the section on Issue II: Utility/ Enablement, are sufficient to also establish patentable utility for U. S. Application Serial No. 60/141,037. Hence, Appellants should be able to rely upon this provisional application to provide an effective filing date of 19 November, 2001 for the instant application.

Issue 2: Utility/ Enablement

Claims 124, 129-131 and 135-145 stand rejected under 35 U.S.C. §101/ 112, first paragraph as allegedly lacking either a specific and substantial asserted utility or a well established utility.

Patentable utility for the PRO1153 polypeptides is based upon the gene amplification data for the gene encoding the PRO1153 polypeptide. The specification discloses that the gene encoding PRO1153 showed significant amplification, ranging from **2.014 to 2.87**-fold in two different lung primary tumors. The Declaration of Dr. Audrey Goddard, submitted with Appellants' Response filed August 25, 2005, explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, the gene amplification levels of **2.014 to 2.87**-fold for lung primary tumors is not a "small increase" as the Examiner contends (page 4 of Final Office action dated October 1, 2004). Appellants also submit that, as any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even with most tumors. Therefore, whether the PRO1153 gene is amplified in few tumor samples or in the vast majority of tumor samples studied is not relevant to its identification as a tumor marker, or its patentable utility. Rather, the fact that the amplification data for PRO1153 is considered significant is what lends support to its usefulness as a tumor marker. Thus, a positive result does indicate the presence of cancer, while a negative result requires further follow up testing, testing which is considered routine by one skilled in the art of oncology and is not considered undue.

The Examiner further asserted on page 5 of the Final Office Action mailed October 1, 2004 that amplification of the PRO1153, polynucleotide does not impart a specific, substantial, and credible utility to the PRO1153 polypeptide since, "there is no evidence regarding whether or not PRO1153 mRNA or polypeptide levels are also increased in this cancer." In support of this assertion, the Examiner cited references by Pennica *et al.*, Haynes *et al.* and Hu *et al.*

First of all, the claims are directed to nucleic acids, not polypeptides, therefore, the issue of whether there is a correlation between gene amplification and polypeptide expression levels is irrelevant. One of skill in the art would understand how to use the claimed nucleic acids to

detect amplification of the gene encoding PRO1153, and how to use the gene amplification results to diagnose cancer. Thus the question of whether or not PRO1153 mRNA or polypeptide levels are also increased in these cancers has no relevance to the utility of the claimed nucleic acid molecules. Moreover, the teachings of Pennica *et al.*, Haynes *et al.* or Hu *et al.*, do not conclusively establish a *prima facie* case for lack of utility.

Instead, Appellants submit that based on the gene amplification data and the substantial, credible, asserted utility of the PRO1153 gene in the diagnosis of lung cancer, one of ordinary skill would know exactly how to make and use these claimed nucleic acids for the diagnosis of cancers, without any undue experimentation.

Response to Rejections

ISSUE 1. U.S. Provisional Application No. 60/141,037 Satisfies the Utility Requirement of 35 U.S.C. § 101/ § 112, First Paragraph based on the results of the Gene Amplification assay

Appellants have asserted that U.S. Provisional Application No. 60/141,037, filed November 19, 2001, discloses the gene amplification assay (shown in Example 170 of the instant specification) and establishes patentable utility for the claimed PRO1153 polypeptides.

Appellants submit, for the reasons set forth below under Issue 2 for Utility/ Enablement, that the results of the gene amplification assay disclosed in the specification of U.S. Application No. 60/141,037, provides at least one credible, substantial and specific asserted utility for the claimed PRO1153 polypeptides under 35 U.S.C. §101/§112, first paragraph. Accordingly, Appellants respectfully request that the subject matter of the instant claims be granted the November 19, 2001, priority date of U.S. Provisional Application No. 60/141,037.

ISSUE 2. Claims 124, 129-131 and 135-145 are supported by a credible, specific and substantial asserted utility, and thus meet the utility requirement of 35 U.S.C. § 101/ 112, first paragraph

The sole basis for the Examiner's rejection of Claims 124, 129-131 and 135-145 under this section is that the data presented in Example 170 of the present specification is allegedly insufficient under the present legal standards to establish a patentable utility under 35 U.S.C. § 101 for the presently claimed subject matter.

Claims 124, 129-131 and 135-145 stand further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Appellants strongly disagree and, therefore, respectfully traverse the rejection.

A. The Legal Standard For Utility Under 35 U.S.C. § 101

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*[1] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler,* 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

In *Cross v. Iizuka*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

The case law has also clearly established that Appellants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden to prove that Appellants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11, 12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the

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6 *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

7 *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

8 *Id.*

9 *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

10 *Ibid.*

11 *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

12 *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

13 *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

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[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II (B)(1).

B. Proper Application of the Legal Standard

Appellants respectfully submit that the data presented in Example 170 starting on page 539 of the specification of the specification and the cumulative evidence of record, which underlies the current dispute, indeed support a "specific, substantial and credible" asserted utility for the presently claimed invention.

Example 170 describes the results obtained using a very well-known and routinely employed polymerase chain reaction (PCR)-based assay, the TaqMan™ PCR assay, also referred to herein as the gene amplification assay. This assay allows one to quantitatively measure the level of gene amplification in a given sample, say, a tumor extract, or a cell line. It was well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. Appellants isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9 (pages 539 onwards of the specification), including primary lung and colon cancers of the type and stage indicated in Table 8 (page 546). The tumor samples were tested in triplicates with Taqman™ primers and with internal controls, beta-actin and GADPH in order to quantitatively compare DNA levels between samples (page 548, lines 33-34). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 539, lines 27-29) and also, no-template controls (page 548, lines 33-34). The results of TaqMan™ PCR are reported in ΔCt units, as explained in the passage on page 539, lines 37-39. One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on . Using this PCR-based assay, Appellants showed that the gene encoding for PRO1153 was amplified, that is, it showed approximately 1.01- 1.52 ΔCt units for lung tumors which corresponds to $2^{1.01}$ -$2^{1.52}$- fold amplification in lung tumors, or **2.014 to 2.87**-fold in two different lung primary tumors.

Previously, in the Office Action mailed March 23, 2004 and on page 6 of the Final Office action mailed October 1, 2004, the Examiner stated based on Hittelman *et al.* that "an increase in chromosome number is a common occurrence in cancerous cells and would result in a positive ΔCt measurement in the instant Specification." Appellants partly agree and disagree with this statement.

Hittelman studied premalignant lesions and suggests that epithelial tumors develop through a multistep process driven by genetic instability (see abstract). Hittelman showed that a

subset of the same molecular changes found in associated tumor were also found in premalignant lesions, suggesting that these premalignant lesions might represent precursor lesions for associated tumors, i.e., a manifestation of a multistep tumorigenesis process. (See Hittelman, page 4, last three lines). Appellants therefore submit that, contrary to the Examiner's rejection, the Hittelman reference strongly supports the Appellants position that there is utility in identifying genetic biomarkers in epithelial tissues at cancer risk (also see Hittelman, abstract, line 4-7). Hittelman adds on page 2, fourth paragraph, line 3 that "it is important to identify individuals at significantly increased cancer risk who might best benefit from different types of intervention". Taken together, even if Appellants were to show that the observed PRO1153 gene amplification were due to chromosomal aneuploidy (which Appellants do not contend to), identifying genetic biomarkers like the PRO1153 gene with this aneuploidy is a very important and useful step, according to Hittelman, in identifying individuals at significantly increased cancer risk. Therefore, Hittelman supports at least one utility for the PRO1153 gene, that is, as a genetic biomarker for cancer or precancerous cells. As one skilled in the art would clearly know, early detection of lung cancer provides information in advance about risk assessment, prognosis and therapy for lung cancer.

Further, the Examiner acknowledges that there was a "increase" in DNA, but stated that the increase was "very small" (Office action mailed March 23, 2004). Regarding this rejection Appellants submit that the Examiner seems to be applying a heightened utility standard in this instance, which is legally incorrect. Instead, whether this "increase" is "significant" needs to be addressed. As evidence that the "increase in DNA" in the gene amplification assay is significant, Appellants submitted a Declaration by Dr. Audrey Goddard in the Supplemental response filed August 25, 2005. The Declaration by Dr. Audrey Goddard provides a statement by an expert in the relevant art stating that "fold amplification" values of at least 2-fold are considered significant in the TaqMan™ PCR gene amplification assay. Appellants particularly draw the Board's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay

in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Accordingly, the **2.014 to 2.87**-fold in two different lung primary tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration.

Further Appellants submit that the fact that two lung tumor samples and three colon tumor samples tested positive in this study does not make the gene amplification data, by any means, less significant or spurious. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even, with most tumors. In fact, some tumor markers are useful for identifying rare malignancies. That is, the association of the tumor marker with a particular type of tumor lesion may be rare, or, the occurrence of that particular kind of tumor lesion itself may be rare. In either event, even these rare tumor markers, which may not give a positive hit with most common tumors, have great value in tumor diagnosis, and consequently, in tumor prognosis. The skilled artisan would know that such tumor markers are very useful for better classification of tumors. Therefore, whether the PRO1153 gene is amplified in two lung tumors or in most lung tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather, whether the amplification data for PRO1153 is significant is what lends support to its usefulness as a tumor marker. It was well known in the art at the time of filing of the application that gene amplification, which occurs in most solid tumors like lung cancers, is generally associated with poor prognosis. Therefore, the PRO1153 gene becomes an important diagnostic marker to identify such malignant lung cancers, even if the malignancy associated with PRO1153 molecule is a rare occurrence. Accordingly, the present specification clearly discloses enough evidence that the gene encoding the PRO1153 polypeptide is significantly amplified in certain types of lung tumors and is therefore, a valuable diagnostic marker for identifying certain types of lung cancers.

C. The Utility of the Claimed Nucleic Acids Does Not Depend Upon the Properties of the Encoded Polypeptide

On page 5 of the final Office Action mailed October 1, 2005, the Examiner points out that "there is no evidence regarding whether or not PRO1153 mRNA or polypeptide levels are

also increased in this cancer". The Examiner points out, especially on page 5 of the Final Office Action, that:

> "what is often seen is a lack of correlation between DNA amplification and mRNA levels (Pennica *et al.*) As discussed by Haynes *et al.*, polypeptide levels cannot be accurately predicted from mRNA levels...the literature cautions researches against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (Hu *et al.*)"

Appellants strongly disagree. First of all, Appellants submit that the instant claims are directed to nucleic acids, not polypeptides, therefore, the issue of whether there is a correlation between gene amplification and polypeptide expression levels is irrelevant. One of skill in the art would understand how to use the claimed nucleic acids to detect amplification of the gene encoding PRO1153, and how to use the gene amplification results to diagnose cancer. Thus the question of whether or not PRO1153 mRNA or polypeptide levels are also increased in these cancers has no relevance to the utility of the claimed nucleic acid molecules.

The claimed nucleic acids can be used in cancer diagnosis without any knowledge regarding the function or cellular role of the encoded protein. Appellants submit that the law clearly states that "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *Newman v. Quigg*, 11 USPQ2d 1340 (Fed. Cir. 1989). Accordingly, the disclosure or identification of the mechanism by which PRO1153 is associated with cancer is not required in order to establish the patentable utility of the claimed PRO1153 nucleic acids.

D. A *prima facie* case of lack of utility has not been established

The Examiner further cited Hu *et al.*, to show that " the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissues" (Page 5 of the Final Office action mailed October 1, 2004).

First of all, as discussed above, the increase in DNA copy number for the PRO1153 gene is significant and would not be considered "small" according to the Goddard declaration. Further, contrary to the Examiner's assertion, the cited Hu *et al.* reference does not conclusively establish a *prima facie* case for lack of utility for the PRO1153 molecule. The Hu *et al.* reference is entitled "Analysis of Genomic and Proteomic Data using Advanced Literature Mining" (emphasis added). Therefore, as the title itself suggests, the conclusions in this

reference are based upon statistical analysis of information obtained from published literature, and not from experimental data. Hu *et al.* performed statistical analysis to provide evidence for a relationship between mRNA expression and biological function of a given molecule (as in disease). The conclusions of Hu *et al.* however, only apply to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and cannot be generalized to breast cancer genes in general, let alone to cancer genes in general. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column).

Moreover, the analytical methods utilized by Hu *et al.* have certain statistical drawbacks, as the authors themselves admit. For instance, according to Hu *et al.*, "*different statistical methods*" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). As is well known in the art, different statistical methods allow different variables to be manipulated to affect the resulting outcome. In this regard, the authors disclose that, "Initial attempts to search the literature " using the list of genes, gene names, gene symbols, and frequently used synonyms generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors add that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (emphasis added). Hence, Hu *et al.* had to manipulate certain aspects of the input data, in order to generate, in their opinion, meaningful results. Further, because the frequency of citation for a given molecule and its relationship to disease only reflects the current research interest of a molecule, and not the true biological function of the molecule, as the authors themselves acknowledge, the "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). Therefore, based on these findings, the authors add, "[t]his may reflect *a bias in the literature* to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added). In other words, some molecules may have been underrepresented merely because they were less frequently cited or

studied in literature compared to other more well-cited or studied genes. Therefore, Hu *et al.*'s conclusions are not based on genes/mRNA *in general.*

Therefore, Appellants submit that, based on the nature of the statistical analysis performed herein, and in particular, based on Hu's analysis of only *one* class of genes, namely, the estrogen receptor (ER)-positive breast tumor genes, the conclusions drawn by the Examiner, namely that, "genes displaying a 5-fold change or less (mRNA expression) in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease (in general)" is not reliably supported.

In conclusion, when the proper legal standard is used, a *prima facie* case of lack of utility has not been met based on the cited references Pennica *et al.,* Haynes *et al.* or Hu *et al.* by the Examiner.

On the contrary, Appellants submit that Example 170 in the specification discloses evidence to show that the PRO1153 gene is amplified in certain lung cancers, and is therefore useful in the diagnosis of these cancers.

Thus, based on the asserted utility for the PRO1153 gene in the diagnosis of selected lung tumors, the reduction to practice of the instantly claimed nucleic acid sequence of SEQ ID NO: 350 in the present application (also see pages 220-222), the disclosure of the step-by-step protocols for making and isolating cDNA clones encoding PRO1153 of SEQ ID NO:350 at least in Example 108, page 490 of the specification, the disclosure of a step-by-step protocol for expressing PRO1153 cDNA in appropriate host cells (in Examples 140-143 and page 376, line 12), the step-by-step protocol of the gene amplification assay in Example 170, the skilled artisan would know exactly how to make and use the claimed nucleic acids for the diagnosis of lung cancers. Appellants submit that based on the detailed information presented in the specification and the advanced state of the art in oncology, the skilled artisan would not have found any experimentation associated with testing lung or colon tumors, given the present disclosure, 'undue'.

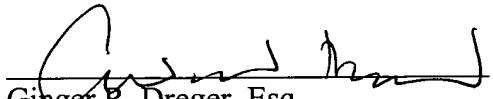
Therefore, since the instantly claimed invention is supported by either a credible, specific and substantial asserted utility or a well-established utility, and since the present specification clearly teaches one skilled in the art "how to make and use" the claimed invention without undue experimentation, Appellants respectfully request reconsideration and reversal of this outstanding rejections under 35 U.S.C. §101 and §112, First Paragraph to Claims 124, 129-131 and 135-145.

CONCLUSION

For the reasons given above, Appellants submit that present specification clearly describes, details and provides a patentable utility for the claimed invention. Moreover, it is respectfully submitted that based upon this disclosed patentable utility, the present specification clearly teaches "how to use" the presently claimed polypeptide. As such, Appellants respectfully request reconsideration and reversal of the outstanding rejection of claims 124, 129-131 and 135-145.

Respectfully submitted,

Date: August 30, 2005



Ginger R. Dreger, Esq.
Reg. No. 33,055

HELLER EHRMAN LLP
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

IX. CLAIMS APPENDIX

Claims on Appeal

124. An isolated nucleic acid comprising:

(a) the nucleic acid sequence of SEQ ID NO: 350;

(b) the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 350; or

(c) the full-length coding sequence of the cDNA deposited under ATCC accession number 209982.

129. The isolated nucleic acid of Claim 124 comprising the nucleic acid sequence of SEQ ID NO: 350.

130. The isolated nucleic acid of Claim 124 comprising the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 350.

131. The isolated nucleic acid of Claim 124 comprising the full-length coding sequence of the cDNA deposited under ATCC accession number 209982.

135. A vector comprising the nucleic acid of Claim 124.

136. The vector of Claim 135, wherein said nucleic acid is operably linked to control sequences recognized by a host cell transformed with the vector.

137. A host cell comprising the vector of Claim 135.

138. The host cell of Claim 137, wherein said cell is a CHO cell, an *E. coli* or a yeast cell.

139. An isolated nucleic acid molecule consisting of a fragment of the nucleic acid sequence of SEQ ID NO: 350, or a complement thereof, of at least 20 nucleotides in length that hybridizes under stringent conditions to:

(a) the nucleic acid sequence of SEQ ID NO:350 or a complement thereof;

(b) the full-length coding sequence of the cDNA deposited under ATCC accession number 209982 or a complement thereof;

wherein, said stringent conditions use 50% formamide, 5X SSC, 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5X Denhardt's solution, sonicated salmon sperm DNA (50 μg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, and washes at 42°C in 0.2X SSC, at 55°C in 50% formamide followed by a high-stringency wash at 55°C in 0.1X SSC, EDTA; wherein said isolated nucleic acid molecule is suitable for use as a PCR primer or probe.

140. The isolated nucleic acid molecule of Claim 139 that is at least 50 nucleotides or above in length.

141. The isolated nucleic acid molecule of Claim 139 that is at least 60 nucleotides or above in length.

142. The isolated nucleic acid molecule of Claim 139 that is at least 70 nucleotides or above in length.

143. The isolated nucleic acid molecule of Claim 139 that is at least 80 nucleotides or above in length.

144. The isolated nucleic acid molecule of Claim 139 that is at least 90 nucleotides or above in length.

145. The isolated nucleic acid molecule of Claim 139 that is at least 100 nucleotides or above in length.

X. EVIDENCE APPENDIX

1. Hittelman *et al.* "Genetic instability in epithelial tissues at risk for cancer," *Ann. NY Acad Sci.* **952**:1-12 (2001).

2. Crowell *et al.* "Detection of trisomy 7 in nonmalignant bronchial epithelium from lung cancer patients and individuals at risk for lung cancer," Cancer *Epidemiol.* **5**:631-637 (1996).

3. Pennica *et al.*, "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors," *Proc. Natl. Acad. Sci. USA* **95**:14717-14722 (1998).

4. Haynes *et al.*, "Proteome analysis: Biological assay or data archive?" *Electrophoresis* **19**:1862-1871 (1996).

5. Federal Register, 2001,Vol. 66, No.4, 1099-1111.

6. Hu *et al.*, "Analysis of genomic and proteomic data using advanced literature mining," *Journal of Proteome Research* **2**:405-412 (2003).

7. Declaration of Audrey Goddard, Ph.D. under 35 C.F.R. 1.132, with attached Exhibits A-G:

A. Curriculum Vitae of Audrey D. Goddard, Ph.D.
B. Higuchi, R. et al., "Simultaneous amplification and detection of specific DNA sequences," *Biotechnology* **10**:413-417 (1992).
C. Livak, K.J., et al., "Oligonucleotides with fluorescent dyes at opposite ends provide a quenched probe system useful for detecting PCR product and nucleic acid hybridization," *PCR Methods Appl.* **4**:357-362 (1995).
D. Heid, C.A. et al., "Real time quantitative PCR," *Genome Res.* **6**:986-994 (1996).
E. Pennica, D. et al., "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors," *Proc. Natl. Acad. Sci. USA* **95**:14717-14722 (1998).
F. Pitti, R.M. et al., "Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer," *Nature* **396**:699-703 (1998).
G. Bieche, I. et al., "Novel approach to quantitative polymerase chain reaction using real-time detection: Application to the detection of gene amplification in breast cancer," *Int. J. Cancer* **78**:661-666 (1998).

Items 1-5 were made of record by the Examiner in the Office Action mailed March 23, 2004.

Items 3-4 and 6 were made of record by the Examiner in the Final Office Action mailed October 1, 2004.

Item 7 was submitted with the Appellants' Response filed on August 24, 2005 and whose entry was indicated as acceptable in a telephone conference with Examiner Wegert on August 24, 2005.